Exhibit 33

Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology

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A number of observational studies (largely case–control) conducted over the last two decades suggest an association between use of talc powders on the female perineum and increased risk of ovarian cancer. A subset of these reports shows a roughly 30–60% increased risk of ovarian cancer associated with perineal talc exposure. A number of researchers partly base their conclusions of an association on the '...chemical relationship between talc and asbestos', the latter substance being a known human carcinogen. Although separating causal from noncausal explanations for an observed statistical association is a difficult process, there currently exist commonly accepted guidelines by which such inferences can be made. These scientific approaches include consideration of the strength of the association, the consistency of the finding across studies, and existence of a biological explanation of the observed phenomenon, among others. When applied to the context of a proposed talc/ovarian cancer association, we conclude that the weak statistical associations observed in a number of epidemiological studies do not support a causal association. ***European Journal of Cancer Prevention*** **20:501–507 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.** (6) Nov.

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Introduction

Ovarian cancer represents a major cause of cancer-related morbidity and mortality in the United States, with an estimated 22 000 new cases diagnosed in 2005 (Boger-Megiddo and Weiss, 2005). It is the seventh most common cancer in women and ranks fourth as a cause of cancer deaths among females from the United States, with some 16 000 succumbing to the disease this year. The lethality of ovarian tumors is in large part because of the fact that clinical symptoms tend to occur late in the natural history of the disease and the lack of screening tests allowing for early diagnosis. In fact, approximately 60% of patients are diagnosed with late-stage disease (stages III and IV), vastly diminishing the chance of long-term survival [approximately 10% at 5 years from diagnosis (Richardson *et al.*, 1985)].

Primary prevention of ovarian cancer remains elusive as a clear etiology for the vast majority of cases is unknown. In 1982, Cramer *et al.* published the first study suggesting a link between use of cosmetic talc and the risk of developing ovarian cancer. Subsequently, a number of additional reports have shown a small but increased risk among women using cosmetic talc products, although this finding is not universal (Chang and Risch, 1997). These statistical associations raise concerns that a cause–effect relationship may exist between talc exposure (particularly perineal use) and ovarian carcinogenesis.

On 13 May 2008, Samuel Epstein, MD, Chairman of the Cancer Prevention Coalition, submitted a Citizen's Petition to the Commissioner of the Food and Drug Administration seeking placement of cancer warning labels on talc products. The Petition requests the Commissioner of Food and Drugs to require that all talc products bear labels with a warning such as, 'Frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer' (Epstein, 2008).

The claim refers to the first observational study (case–control) suggesting an association between the use of talc powders on the female perineum (by direct dusting or dusting sanitary napkins) and increased risk of ovarian cancer, published in 1982. In this document, the researchers partly base their conclusions of an association on the "...chemical relationship between talc and asbestos", the latter substance being a known human carcinogen. The claim also references a number of additional epidemiological studies conducted after 1982 that have shown a statistical link between talc dusting and ovarian cancer risk. A subset of these reports show a roughly 30–60% increased risk of ovarian cancer associated with perineal talc exposure.

The issues articulated by Epstein *et al.* in relation to the possible carcinogenicity of talc are not uncommon when dealing with interpretation of results derived from observational studies. In a study published 20 years ago, Feinstein provided an insightful and cogent explanation for the myriad problems that plague the process of causal inference as it applies to nonexperimental data (Feinstein, 1988). As he

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points out, most people learn about science by studying experimental methods. These methods largely include direct intervention by the experimenter on whatever entity is under study, whether it be an animal species such as rats or mice, specific chemical compounds, subatomic particles, etc. The scientist, in this context, directly manipulates the study subject/object using established principles of experimental science. In the context of human studies, the experimental design that has come to represent the 'gold standard' of cause–effect relationships is the randomized clinical trial. Unfortunately, in epidemiological research, issues of feasibility and ethical considerations preclude randomization of healthy human participants to receive potentially harmful exposures to various substances, including those that represent possible carcinogenic hazards. Therefore, the epidemiologist must substitute observational methods to study cause–effect relationships that preclude direct intervention with, and/or manipulation of, study participants (i.e. experiments). Owing to this fact, criteria for establishing cause–effect relationships are inherently different when using epidemiological methods versus experimental ones.

In 1965, Hill published a landmark study articulating standards for drawing causal inferences from observational data. His rationale for this stemmed from the realization that the urgency of many public health problems demands action despite the fact that existing knowledge might be imperfect (Rothman, 1986). The 'Hill Criteria' as they have become known, are not simply a 'checklist' of requirements that must be met in order to determine cause–effect relationships. Rather, they represent a theoretical framework to guide one's thinking when attempting to decide whether a body of data meets a basic threshold necessary to distinguish causal from noncausal associations. These criteria include: (i) strength of association, (ii) consistency (i.e. repeated observation of an association in different populations under different circumstances), (iii) specificity (a given cause leads to a specific effect), (iv) temporality (cause must precede effect), (v) biological gradient (dose–response), (vi) plausibility (biological plausibility), (vii) coherence (i.e. that a given cause–effect relationship for an association does not conflict with what is known of the natural history and biology of the disease in question), (viii) experimental evidence (to support the observational findings), and (ix) analogy.

Although the Hill criteria do not provide a complete solution to the dilemma of causal inference in epidemiology, their importance lies in establishing at least a general framework for the process. The proposed talc/ovarian cancer association represents an illustrative example of the utility of this framework. Below we discuss the points raised by Epstein *et al.* in this context and show that the conclusion that the proposed talc/ovarian cancer association is causal is not supported by existing data.

Talc and ovarian cancer: overview of the scientific evidence

The possibility that perineal talc exposure could be associated with development of ovarian cancer was initially derived from a case–control study published in 1982 (Cramer *et al.*, 1982). Since that time, a number of additional reports have addressed this question, with most showing odds ratios (OR) ranging between 1.0 and 2.0 (Table 1). Although this has prompted some to suggest that these estimates of effect provide support for a cause–effect relationship between this exposure and disease outcome, several important caveats must be considered.

Effects of this magnitude are often characterized as 'weak effects' and although the exact definition of a weak effect is debatable, most epidemiologists would consider associations of less than 2.0 to fall within this general category. Hill and others argue that strong associations are more likely to be causal than weak associations as, '...if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident' (Rothman, 1986). As Rothman points out, weak associations are more likely to be explained by undetected biases.

Measures of association of this magnitude are often difficult to interpret. This is based on the fact that the investigator cannot directly manipulate the levels of exposure of interest or extraneous factors that could affect study findings. Attempts to control for external factors are accomplished by statistical manipulations of collected data. However, this process depends on the accuracy and completeness of data collection. Further, the correct choice and interpretation of both statistical models and statistical findings can also be contentious.

It is important to point out that although an association is weak, this does not rule out a causal connection. Nonetheless an example of a factor that could confound the weak effect shown for perineal talc is smoking. It is now recognized that smoking is a risk factor for a number of solid tumors including lung cancer (with ORs on the order of 5.0 vs nonsmokers) and esophageal cancer. Evidence exists that smoking may also be related to at least some types of ovarian tumor, in particular those of the mucinous histology (Huncharek *et al.*, in press). The current literature contains a number of reports showing a doubling or tripling of mucinous ovarian cancer risk among smokers (Green *et al.*, 1997; Pan *et al.*, 2004). Interestingly, in a recent meta-analysis of observational studies, Huncharek *et al.* (in press) show that smoking not only increases the risk of mucinous ovarian tumors, but also the more common serous tumors (Table 2). As Rosenblatt *et al.* (1998) reported that smokers are more likely to engage in perineal talc dusting compared with nonsmokers, an imbalance in smokers across case and control groups in epidemiological studies of the talc/ovarian cancer association could contribute to a spurious positive association.

Table 1 **Overview of observational studies examining perineal talc use/ovarian cancer risk**

Reference	Number of cases	Number of controls	Frequency of powder use	OR (95% CI)	Hospital vs. population based study
Booth *et al.* (1989)	235	451	Never vs. ever	1.29 (0.92–1.80)	H
Chang and Risch (1997)	450	564	None vs. any	1.42 (1.08–1.86)	P
Chen *et al.* (1992)	112	224	Never vs. ever	3.9 (0.9–10.6)	P
Cook *et al.* (1997)	313	422	None vs. any	1.5 (1.1–2.0)	P
Cramer *et al.* (1999)	563	523	Never vs. any	1.60 (1.18–2.15)	P
Cramer *et al.* (2005)	215	215	None vs. any	1.92 (1.27–2.89)	P
Gertig *et al.* (2000)[a]	307		Never vs. ever	1.05 (0.84–1.32)	P
Godard *et al.* (1998)	170	170	Never vs. ever	2.49 (0.94–6.58)	P
Harlow *et al.* (1992)	235	239	Never vs. any	1.5 (1.0–2.1)	P
Harlow *et al.* (1992)	116	158	None vs. any	1.1 (0.7–2.1)	P
Ness and Cottreau (1999)	767	158	None vs. any	1.5 (1.1–2.0)	P
Purdie *et al.* (1995)	824	860	Never vs. ever	1.27 (1.04–1.54)	P
Rosenblatt *et al.* (1998)	77	46	Never vs. any	1.0 (0.2–4.0)	H
Tzonou *et al.* (1993)	189	200	Never vs. any	1.05 (0.28–3.98)	H
Whittemore *et al.* (1998)	188	539	Never vs. ever	1.45 (0.81–2.60)	H
Wong *et al.* (1999)	499	755	Never vs. ever	1.0 (0.8–1.3)	H

CI, confidence interval; H, hospital-based study; OR, odds ratio; P, population-based study.
[a]Cohort study.

Table 2 **Summary of meta-analysis results**

Risk category	Number of studies	RRs	Statistically homogeneous?
Current/ever smoker	Three cohorts	1.14 (0.93–1.35)	Yes
Current/ever smoker	20 case–control	1.06 (1.01–1.12)	No
Highest vs. lowest pk/years	10 studies (three cohort, seven case–control)	1.21 (1.10–1.31)	No
As above, excluding three studies that combined both borderline and invasive tumors	Seven studies total	1.11 (1.00–1.22)	Yes
Analysis stratified by tumor histology			
Serous tumors			
Current/ever smoker	Four studies	1.28 (0.95–1.61)	Yes
Serous/nonmucinous/other histologies			
Current/ever smoker	Six studies	1.31 (1.15–1.47)	Yes
Mucinous tumors			
Current/ever smoker	Six studies	2.58 (2.23–2.93)	Yes

Pk/years, packs smoked per year; RRs, summary relative risk.

Consistency of an effect could contribute to a causal claim despite a finding of a weak association. Epstein *et al.* characterize the talc/ovarian cancer relationship as being 'confirmed' by multiple scientific publications as well as by review of available evidence by the International Agency for Research on Cancer. They state that, '...International Agency for Research on Cancer concluded that eight publications confirmed a 30–60% increased risk of ovarian cancer following the perineal application of talc'. Despite the claims of the petitioners, a review of available evidence shows that the epidemiological evidence is not consistent across studies or across study types. For instance, Table 1 shows several inconsistencies in the database. Clearly, not all studies showed a positive, statistically significant association, even among the case–control studies that make up the bulk of the database. In addition, there was relatively wide variation in the magnitude of measures of association.

Interestingly, up to the date of filing of the petition by Epstein *et al.*, only one cohort study had been published, that of Gertig *et al.* (2000) that showed no association between perineal talc use and ovarian cancer risk. Given the conflicting findings of case–control studies, Huncharek *et al.* (2003) used meta-analytic techniques to explore possible sources of variability among these reports. Their rationale for doing so was that if meta-analyses showed that the patterns of low relative risks or ODs are consistent across all relevant studies in different populations, these weak associations are less likely to be due to confounding or other biases. If a statistical test for heterogeneity shows effects of different magnitudes across studies, sensitivity analyses can be employed to determine the source of observed variability and thereby identify biases due to study design, case–control selection, etc.

Huncharek *et al.* initially pooled data from 15 case–control and one cohort analysis, yielding a summary relative risk (RRs) of 1.33 (1.16–1.45). Although this suggests a statistically significant positive association between perineal talc use and ovarian cancer risk, sensitivity analyses demonstrated clear differences in outcome based on study

design. That is, hospital-based case–control studies showed no evidence of an effect [1.19 (0.99–1.41)] in contrast to those reports using population-derived controls [1.38 (1.25–1.52)]. More frequent talc use among hospital-based control participants versus population-derived controls does not explain this finding, as the proportion of controls using talc was the same in both groups, that is, 32%. Other factors account for this difference in outcome. These findings suggest bias and bring the validity of the initial pooled RRs into question. The Huncharek report provides some possible explanation for the observed differences and indicates that study outcomes are not consistent. It is possible that the potentially spurious positive association between talc use and ovarian cancer risk is the existence of a 'treatment effect' among cases. Particularly among population-based studies, a varying proportion of cases will be prevalent rather than incident. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy, and/or surgery. Side effects from treatment may prompt talc use among some patients. Although many questionnaires used in case–control studies may specify talc use before diagnosis, patients may not always make the distinction between prediagnosis and posttreatment use. Exposure misclassification among 'prevalent' cases may cause a spurious finding of an association when none, in fact, exists.

Further supporting the findings of this meta-analysis are the more recent and updated pooled data provided by Langseth *et al.* (2008) cited by the Epstein petition. These researchers pooled data from 20 relevant epidemiological studies. Again, although the calculated summary RR obtained from pooling data from all 20 reports gives a statistically significant RRs (pooled odds ratio) of 1.35 (1.26–1.46), the statistical test for data heterogeneity yielded a P value of 0.036. A P value of this size (i.e. < 0.10) is indicative of significant heterogeneity and, as per convention (Petitti, 2000), precludes statistical pooling, that is the pooled summary estimate of effect is not valid given that the data are heterogeneous. This shows that the available data are not consistent and therefore makes a causal association less likely.

One of the more persistent findings among the epidemiological studies examining this suspected association is the lack of a dose–response relationship. Table 3, derived from data presented in the meta-analysis by Huncharek *et al.*, displays dose–response data for those included studies providing such information. Many of the reports do not show increased risk with increasing exposure. The even more problematic finding in terms of establishing a causal association is that a number of studies suggest that risk decreases with increased exposure (Huncharek *et al.*, 2003).

Few researchers directly address the above-noted lack of evidence of a dose–response relationship. Huncharek *et al.* (2003) and Huncharek and Muscat (2007), in contrast, offer a number of possible explanations for an inverse

Table 3 Talc dose–response data for perineal application and ovarian cancer risk

Reference	Years of talc use/ OR + 95% CI	Number of talc applications per month/OR + 95% CI
Booth *et al.* (1989)	NG	1 0.7 (0.3–1.8)
		4 2.0 (1.3–3.4)
		30 1.3 (0.8–1.9)
Chang and Risch (1997)	<30 1.7 (1.09–2.68)	<10 1.84 (1.24–2.73)
	30–40 1.44 (0.96–2.15)	10–25 1.13 (0.74–1.72)
	>40 0.96 (0.54–1.38)	>25 0.95 (0.61–1.49)
Cook *et al.* (1997)	0–5.5 1.8 (0.9–3.5)	NG
	5.5–13.5 1.6 (0.9–2.9)	NG
	13.5–27 1.2 (0.6–3.4)	NG
	>27 1.8 (0.9–3.4)	NG
Cramer *et al.* (1999)	<20 1.9 (1.2–3.0)	<30 2.2 (1.4–3.6)
	20–30 1.3 (0.8–2.3)	30–39 1.2 (0.81.8)
	>30 1.4 (0.9–2.3)	40+ 1.6 (0.8–3.1)
Gertig *et al.* (2000)	NG	4–24 0.99 (0.67–1.46)
		≥ 30 1.12 (0.82–1.55)
Harlow *et al.* (1992)	<10 1.2 (0.5–2.6)	<5 1.5 (0.8–2.7)
	10–29 1.6(1.0–2.7)	5–29 1.2 (0.6–2.2)
	≥ 30 1.6 (1.0–2.7)	≥ 30 1.8 (1.1–3.0)
Ness and Cottreau (1999)	1 2.0 (1.0–4.0)	NG
	1–4 1.6 (1.1–2.3)	
	5–9 1.2 (0.8–1.9)	
	10+1.2 (1.0–1.5)	
Whittemore *et al.* (1998)	1–9 1.60 (1.00–2.57)	1–20 1.27 (0.82–1.96)
	10+1.11 (0.74–1.65)	>20 1.45 (0.94–2.22)
Wong *et al.* (1999)	1–9 0.9 (0.6–1.5)	NG
	10–19 1.11 (0.74–1.65)	
	≥ 20 0.9 (0.6–1.2)	

CI, confidence interval; NG, not given; OR, odds ratio.

dose–response relationship. As outlined above, treatment for ovarian cancer may induce specific symptoms that could prompt short-term talc use. For instance, some early stage patients may undergo radiation therapy, which causes skin irritation. Such side effects could result in some patients using talc products to address these side effects. Talc is often recommended to keep skin folds in the perineum dry and prevent skin breakdown secondary to radiation. In addition, symptoms of the disease process itself could cause some women to use talc to counter these symptoms. Paulsen *et al.* (2005) and Golf *et al.* (2004) document that a number of symptoms are quite common among ovarian cancer cases versus control participants. For instance, Golf *et al.* show that increased abdominal size is over seven times more common among cases versus controls, whereas abdominal bloating is 2.5 times more common. The combination of bloating, increased abdominal size and urinary symptoms were found in almost half of all patients with ovarian cancer, but in only 8% of controls. In addition, of interest are the findings by Green *et al.* (1997) that increased ovarian cancer risk was seen among patients with painful periods or excessive vaginal bleeding. Again, such symptoms

could prompt talc use and lead to a spurious association with talc. Although there are no firm data in the existing literature to definitively establish that these factors lead to increased short-term use of talc, the scenarios are plausible and could explain the inverse dose–response relationship seen in a number of epidemiological studies.

The majority of reports largely ignore the counterintuitive findings, although Cramer *et al.* (1999) attribute the dose–response inconsistencies, possibly to the 'crudeness' of the exposure measurement used. What is not acknowledged is that this same problem of imprecise exposure estimates could also explain a spurious positive association of talc and ovarian cancer, especially in light of the inconsistent outcomes across reports. In summary, the failure to show a coherent and consistent relationship between talc exposure and ovarian cancer risk argues against a causal association.

An additional limitation of the existing literature dealing with the proposed talc/ovarian cancer association is the lack of any known biological mechanism through which talc particles could induce ovarian tumors. This represents probably the most troublesome aspect of arguments in support of this proposed causal association. It is also interesting to note that biological theories put forth to explain how talc may cause neoplastic transformation have changed over time as various proposed mechanisms have met with criticism in the developing literature.

Initially, Cramer *et al.* (1982) and others sought to draw an analogy between talc and fibrous asbestos, the latter being a known and well-described carcinogen. The biological effects of asbestos have been elucidated over the last 50–60 years by a multitude of epidemiological, in-vitro and in-vivo studies (Huncharek, 1986). Specific asbestos types are recognized as both animal and human carcinogens and, because of this fact, this commodity is banned from use in the United States.

A number of investigators initially implicated talc products as possible carcinogens, as before the early 1970s some talc products contained small amounts of asbestos fibers (Rohl *et al.*, 1976). Clearly, such products could possibly represent a carcinogenic risk secondary to the asbestos contamination. It should be pointed out that this in no way implicates talc as a toxin as the problematic constituent of such products was the asbestos fibers, not talc.

Since the early 1970s, the relevant industries voluntarily eliminated asbestos contamination from talc products. On account of this, the 'antitalc' argument shifted to implicate talc itself as a carcinogenic risk based on its 'chemical similarity' to asbestos. It is interesting, and confusing, as to why talc is thought by some to be carcinogenic based on the fact that there are some common chemical constituents of talc and asbestos.

Both commercial talc and the group of minerals known as asbestos are magnesium silicates. Beyond that fact, the two substances share no common characteristics. The work by Stanton *et al.* (1981) shows that the carcinogenic ability of fibrous asbestos is due to its structure, not its chemical composition. Although talc and asbestos are both magnesium silicates, they are structurally distinct and belong to different mineral groups and subgroups, as detailed by Muscat and Huncharek (2008). Amphibole asbestos minerals are inosilicates while talc is a member of the silicate subclass phyllosilicate and group clay or montmorillonite/smectite. Although serpentines, including serpentine asbestos (chrysotile), are also phyllosilicates, serpentine minerals belong to the kalolinite–serpentine group. The asbestos varieties of serpentine are structurally different from other members of the serpentines in that their brucite layers and silicate layers bend into tubes that produce fibers. Nonfibrous serpentine does not have carcinogenic properties and it is clear that the physical structure of serpentine asbestos (and amphibole asbestos) is responsible for its disease-causing potential, not its atomic constituents. It simply does not follow that one should assume talc is carcinogenic simply because it is a silicate. Structure, not chemical composition, dictates toxicity/carcinogenicity.

Given the dissimilarities between talc and asbestos with regard to their fibrous shapes, the weak but increased associations in the epidemiological studies could be attributed to other mechanisms, assuming that the statistical associations are unbiased and not due to confounding. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response (Ness and Cottreau, 1999). Pelvic inflammatory diseases, however, such as endometriosis, peritonitis, tuboovarian abscess formation, etc., have not been associated with an increased risk of ovarian cancer. A meta-analysis of studies of antiinflammatory drug use found no reduction in ovarian cancer risk (Bonovas *et al.*, 2005). In fact, the study by Merritt *et al.* (2008) that was cited by Epstein *et al.* also showed no relationship between inflammation and ovarian cancer risk.

Most recently, Cramer *et al.* (2005) proposed that the talc/ovarian cancer association might be explained by the induction of anti-MUC1 antibodies. This idea has been debated on statistical grounds in which talcum powder applied to the perineum was associated with increased anti-MUC1 expression but the correlation was also observed when talc powder was applied to other body parts. More importantly, the simple observation that talc elevates immunoglobulin protein levels in blood, possibly by heat shock proteins, seems to have no known direct relevance for ovarian cancer, as anti-MUC1 is associated with other cancers and because there is no known role of heat shock proteins in ovarian cancer risk.

Some of the most important biological data supporting the nontoxic nature of talc come from the clinical use of talc in treating both malignant and benign pleural effusions in humans (i.e. pleurodesis). This is a common procedure in the United States and elsewhere and talc slurry is applied directly to the pleura (through chest tube placement) to induce obliteration of the pleural space by scarring and prevent the reaccumulation of fluid secondary to tumor or benign causes. Multiple long-term clinical studies, as reviewed by Muscat and Huncharek (2008), have not shown a single case of cancer secondary to direct talc application to the human pleura (Shaw and Agarwal, 2004). There are also data showing that talc has demonstrated antitumor properties secondary to the induction of endostatin when used in pleurodesis (Najmunnisa *et al.*, 2007). In fact, patients with pleurodesis treated with talc are known to experience longer survival times than those treated with other sclerosing agents. This is likely due to the tumor-inhibitory effects of talc.

Finally, other human data, such as the demonstration that talc inhaled in mining and milling operations is not associated with increased pulmonary tumors, and the likelihood that talc could selectively induce ovarian cancer and not lung cancer at exposure concentrations orders of magnitude lower than that experienced in occupational settings, argue against its toxicity (Muscat and Huncharek, 2008).

Although the process of drawing causal inferences from scientific data is complex, application of accepted standards, as noted above, to the talc/ovarian cancer relationship clearly indicates that the available epidemiological and other evidence does not support a causal connection. The weak association shown in a subset of observational studies can potentially be explained by numerous alternative hypotheses, as detailed throughout this document. Given the lack of supporting evidence from in-vivo, in-vitro, and clinical research studies using human participants, the weak epidemiological association is unlikely to be causal.

Summary

Although separating causal from noncausal explanations for an observed statistical association is a difficult process, there currently exist commonly accepted guidelines by which such inferences can be made. These scientific approaches include consideration of the strength of the association, the consistency of the finding across studies, and existence of a biological explanation of the observed phenomenon, among others. When applied to the context of a proposed talc/ovarian cancer association, we conclude that the weak statistical associations cited in the petition do not support a causal association.

These conclusions are based on a number of statistical, methodological, and biological issues. First, contrary to the assertions of Epstein (2008), findings from the cited studies are not consistent from study to study, and also differ by study design. Two meta-analyses by Huncharek *et al.* (2003) and Langseth *et al.* (2008) both show significant differences in summary ORs between population-based and hospital-based case–control studies, with the latter showing generally null results. The Nurses Health Study, the one prospective study that examined this association, found no risk with talc dusting. Formal statistical tests for heterogeneity in both analyses support this finding. This fact suggests the existence of bias, and standard approaches to meta-analysis indicate that the pooled OR, in this case an OR of 1.30, is not valid in the presence of heterogeneity. Huncharek and Muscat (2007) suggest multiple possible sources of bias that could produce a spurious positive finding, including unaccounted for effects of cancer treatment and confounding by smoking.

The assembled data also fail to show a clear dose–response relationship, that is, increasing ovarian cancer risk with increasing talc exposure. Some epidemiological studies actually suggest an inverse association between perineal talc exposure and cancer risk. The reasons for this inverse association in some studies are not known, but could be due to aspects of talc usage that are not fully understood such as the possibility that disease symptoms or cancer treatment may spur temporary talc use in case patients.

There is no coherent biological explanation as to how talc could induce cancer of the ovary. The theories put forth to explain the statistical association between talc and ovarian cancer have changed over time with little underlying consistency. The long-standing claim that talc is chemically 'similar' to asbestos and is therefore a carcinogen is a misunderstanding of the chemical and physical properties of talc.

The use of therapeutic talc for pleurodesis in patients with benign and malignant pleural effusions involves the direct application of talc to the human pleura. Clinical follow-up studies of these patients have shown no increased incidence of lung or pleural malignancies despite patient follow-up extending over decades. The above-noted data are supported by the lack of positive findings among occupational cohorts exposed to talc, and negative findings from various animal studies. More recently proposed mechanisms based on other biological pathways are speculative at this point. Given the lack of supporting evidence from in-vivo and clinical research studies using human participants, the weak and inconsistent epidemiological associations, that also lack a gradient in effect, argue against a claim of causality.

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Conflicts of interest

Drs. Huncharek and Muscat were consultant to Johnson and Johnson Consumer Product Worldwide at the time initial drafts of this manuscript were produced.

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